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PII: S0002-9378(20)30614-1

DOI: https://doi.org/10.1016/j.ajog.2020.05.058

Reference: YMOB 13290

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 20 December 2019

Revised Date: 7 May 2020

Accepted Date: 29 May 2020

Please cite this article as: van der Kooi A, Mulder R, Hudson M, Kremer L, Skinner R, Constine L, van Dorp W, van Dulmen-den Broeder E, Winther JF, Wallace W, Waugh J, Woodruff TK, Anderson RA, Armenian S, Bloemenkamp K, Critchley H, Demoor-Goldschmidt C, Ehrhardt M, Green D, Grobman W, Iwahata Y, Krishna I, Laven J, Levitt G, Meacham L, Miller E, Mulders A, Polanco A, Ronckers C, Samuel A, Walwyn T, van den Heuvel-Eibrink M, Levine J, Counseling and surveillance of obstetric risks for female childhood, adolescent, and young adult cancer survivors: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group, *American Journal of Obstetrics and Gynecology* (2020), doi: https://doi.org/10.1016/j.ajog.2020.05.058.

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Disclosure statement: The authors report no conflict of interest.

Word count:
Abstract: 351
Main text: 4094

Condensation: Female cancer survivors have increased risks of premature delivery and low birth weight associated with radiotherapy exposing the uterus, which warrant high-risk pregnancy surveillance.

Running head: IGHG recommendations for management of obstetric risks for female CAYA survivors

AJOG at a glance:

Why was this study conducted? National guidelines that identify specific adverse pregnancy outcomes and the clinical characteristics of childhood, adolescent, and young adult (CAYA) cancer survivors are scarce and vary in content.

What are the key findings? There are increased risks of premature delivery and low birth weight associated with radiotherapy exposing the uterus and pregnancy-related cardiomyopathy following treatment with anthracyclines.

What does this study add to what is already known? This guideline from the International Late Effects of Childhood Cancer Guideline Harmonization Group identifies specific adverse obstetric related outcomes that are increased in CAYA cancer survivors, to characterize the population that will benefit specifically from an individualized preconception consultation and pregnancy surveillance.

Keywords: prenatal care; late effects; childhood cancer survivors; fecundity; pregnancy;

ABSTRACT

Objective: Female childhood, adolescent, and young adult (CAYA) cancer survivors have an increased risk of adverse pregnancy outcomes related to their cancer or treatment-associated sequelae. Optimal care for CAYA cancer survivors can be facilitated by clinical practice guidelines that identify specific adverse pregnancy outcomes and the clinical characteristics of at-risk subgroups. However, national guidelines are scarce and vary in content. Here, the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) offers recommendations for the counselling and surveillance of obstetric risks of CAYA survivors.

Data sources: A systematic literature search in MEDLINE (through PubMed) to identify all available evidence published between January 1990 and December 2018.

Study eligibility criteria: Published articles on pregnancy, perinatal or congenital risks in female cancer survivors were screened for eligibility. Study designs with a sample size larger than 40 pregnancies in CAYA cancer survivors (diagnosed before age 25, not pregnant at that time) were eligible.

Study appraisal and synthesis methods: This guideline from the IGHG systematically appraised the quality of available evidence for adverse obstetric outcomes in CAYA cancer survivors using GRADE methodology, and formulated recommendations to enhance evidence-based obstetric care and preconception counseling of female CAYA cancer survivors.

Results: Healthcare providers should discuss the risk of adverse obstetric outcomes based on cancer treatment exposures with all female CAYA cancer survivors of reproductive age, before conception. Health care providers should be aware that there is no evidence to support an increased risk of giving birth to a child with congenital anomalies (high quality

evidence). Survivors treated with radiotherapy to volumes exposing the uterus and their health care providers should be aware of the risk of adverse obstetric outcomes including miscarriage (moderate quality evidence), premature birth (high quality evidence) and low birth weight (high quality evidence); therefore, high risk obstetric surveillance is recommended. Cardiomyopathy surveillance is reasonable prior to pregnancy or in the first trimester for all female survivors treated with anthracyclines and/or chest radiation.

Conclusions: Female cancer survivors have increased risks of premature delivery and low birth weight associated with radiotherapy targeting the lower body and thereby exposing the uterus, which warrant high-risk pregnancy surveillance.

INTRODUCTION

Five year survival rates for childhood, adolescent, and young adult (CAYA) cancer patients now approach 80%[1]. Consequently, increasing numbers of CAYA cancer survivors are at risk for adverse physical and psychosocial complications from their cancer and/or its treatment[2]. Reproductive health, and specifically pregnancy and delivery outcomes, represent a critical area for long-term follow-up as having children is an important determinant of quality of life for CAYA cancer survivors[3-7].

Previous research indicates difficulty conceiving or carrying a pregnancy to term, as well as excess risk of adverse pregnancy outcomes, among CAYA cancer survivors . For example, the risks of premature birth and postpartum hemorrhage are higher in CAYA cancer survivors compared to women who did not have cancer[8-13], and these risks are further increased in survivors treated with abdominopelvic radiotherapy[9, 11-14]. Evidence-based clinical guidelines on surveillance in pregnancy can identify the type and prevalence of specific obstetric and perinatal complications, characterize the clinical features of those at risk, help survivors make informed decisions, facilitate counseling and timely referral to high-risk obstetric care, and enable opportunities for interventions to optimize pregnancy outcomes.

OBJECTIVE

Published clinical practice guidelines by North American and European cancer groups reference general obstetric risks [15-18], but do not comprehensively assess the clinical features of those who could benefit from high-risk obstetric follow-up. Herein, we summarize the results of a systematic review undertaken by the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) and present a critical appraisal of available evidence on obstetric risks in CAYA cancer survivors, synthesizing these findings into

evidence-based recommendations for surveillance and counseling of CAYA cancer survivors during pregnancy and delivery due to their cancer or cancer treatment.

METHODS

This guideline focuses on facilitating timely identification of CAYA cancer survivors at high-risk of obstetric complications diagnosed with cancer before age 25 years (and not pregnant at that time) who would benefit from preconception counseling and surveillance during pregnancy. Management of obstetric complications is beyond the scope of the present guideline, which should defer to standards established by local/national health systems. Standardized definitions used in this guideline are presented in **Appendix 1**.

The obstetric guideline panel consisted of 33 experts from the United States of America, United Kingdom, Denmark, Germany, France, New Zealand, Australia, Japan and the Netherlands from relevant disciplines, including gynecology, obstetrics, midwifery, endocrinology, pediatric oncology, radiation oncology, epidemiology, and guideline methodology, as well as CAYA survivor/family representatives.

Methods of the IGHG have been described previously[19]. For this guideline, concordances and discordances across existing survivorship guidelines of the North American Children's Oncology Group (COG)[15], the Dutch Childhood Oncology Group (DCOG)[16], the Scottish Intercollegiate Guidelines Network (SIGN)[18], and the UK Children's Cancer and Leukaemia Group (UKCCLG)[17] were evaluated. We defined the major outcomes for obstetric problems in survivors and congenital problems in offspring (**Appendix 1**). For all discordances and relevant outcomes, focused clinical questions were formulated to determine whether specific preconception consultation or surveillance was indicated. Four working groups evaluated the following topics: 1) adverse fetal outcomes in pregnancy (such as miscarriage);

2) adverse maternal outcomes in pregnancy; 3) delivery outcomes; and 4) congenital anomalies of the neonate.

A systematic literature search was performed in MEDLINE (through PubMed) to identify all available evidence published between January 1990 and December 2018, using the search terms “childhood cancer”, “survivors”, “late effects” and “obstetric problems”. Details of the full search strategy are included in **Appendix 2**. All study designs with a sample size larger than 40 pregnancies in female childhood cancer survivors were eligible. To ensure rigorous review of manuscripts by at least two individuals, only studies published in English were selected for analysis. All abstracts were screened by two independent reviewers (ALLFK and one working group member). Disagreements were resolved through consensus. Cross-reference checking was performed to identify additional studies overlooked during the initial search. Relevant articles were summarized in one evidence table by two reviewers (ALLFK and one working group member), including a critical appraisal of risks of bias **(Appendix 3).** The evidence tables were subsequently assembled into summary of findings tables (ALFFK) and revised where necessary (RLM, LCMK). We assessed the quality of the body of evidence for each clinical question according to criteria based on Grading of Recommendations Assessment Development and Evaluation (GRADE)[20] (**Appendix 4**). The quality of the total body of evidence is graded according to four levels: High (⨁⨁⨁⨁), further research is unlikely to change the confidence in the estimate of effect; Moderate (⨁⨁⨁⊖), further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate; Low (⨁⨁⊖⊖), further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate; and Very low (⨁⊖⊖⊖), any estimate of effect is very uncertain. The level of evidence decreased in the presence of study limitations (risk of bias in the studies),

inconsistency of results between studies, indirectness of the study populations or outcomes, or imprecision of the effect estimates. The level of evidence increased if the effect sizes were large or there was evidence for a dose-response relationship.

Translating evidence into recommendations

Recommendations were drafted considering the level of the evidence, other effects of the expected risks (such as unnecessary medicalization), and the need for flexibility across health care systems [21]. Terminology employed for radiotherapy and obstetric outcomes can be found in **Appendix 5**. Decisions were made through iterative group discussions, final recommendations represent unanimous consensus. The strength of the recommendations was graded according to published evidence-based methods **(Appendix 4).** Recommendations were classified into strong or moderate recommendations, and based on high quality evidence, moderate quality evidence or expert opinion[19, 21, 22]. Pregnancy care-related recommendations from the IGHG cardiomyopathy guideline were adopted in this guideline to provide a complete overview of recommendations for pregnancy surveillance. The final harmonized recommendations were critically appraised by four independent external experts in the field and two survivor representatives.

RESULTS

Discordances across existing LTFU guidelines

Identification of concordances and discordances amongst existing surveillance recommendations is displayed in **Appendix 6**. The literature search yielded 2,772 abstracts for pregnancy and delivery related risks and 2,492 abstracts for congenital anomalies. In total, 98 full texts were reviewed, and 28 articles were included (**Figure 1, included articles**

in Appendix 7). The evidence tables and summary of findings are presented in **Appendix 8**. The conclusions of evidence tables including GRADE assessment are summarized in **Table 1** and **Appendix 9** and depicted in a color scheme in **Appendix 10**.

Who needs preconception consultation or specific obstetric surveillance?

Evidence for risks during pregnancy

Miscarriage

There is moderate level evidence that CAYA cancer survivors treated with radiotherapy to volumes exposing the uterus are at increased risk of miscarriage compared to the general population[9, 14, 23-29]. However, this association was only borderline significant in a large cohort from the British Childhood Cancer Survivor Study (BCCSS)[26] and not significant in two smaller studies[24, 28]. There is only low level evidence for a dose-response relationship[29, 30]. The evidence indicated no significant effect due to chemotherapy[9, 26, 30, 31].

Termination of pregnancy

There is no data indicating an increased risk of medically-induced terminations (very low level evidence)[14, 23, 26, 29, 32] among CAYA cancer survivors in general. However, there is (very) low level evidence for an increased risk for termination of pregnancy after any radiotherapy[14, 26] and chemotherapy[14, 26]. Of note, these findings are compromised by terminology in the relevant reports that limits the distinction between medically-indicated and elective termination of pregnancy.

Stillbirth

There is no data indicating an increased risk of stillbirth (moderate level evidence) in CAYA cancer survivors in general[9, 29], and low level evidence for increased risk of stillbirth after moderate to high doses of ovarian-uterine radiotherapy (>10 Gy)[33] or abdominopelvic radiotherapy (>25 Gy)[30].

Gestational hypertension

There is very low level evidence for an effect of radiotherapy on the risk of gestational hypertension in CAYA cancer survivors as compared to survivors treated without radiotherapy. The increased risk was only reported in the abdominopelvic irradiated survivors who had been diagnosed with Wilms tumor in the BCCSS[34], while two smaller studies did not find this association[13, 35]. A paper from the National Wilms Tumor Study Group observed an increased risk of any hypertensive disorder of pregnancy with increasing doses of flank radiotherapy, but as this was the only identified study assessing radiotherapy dose, the level of evidence is very low.

Pre-eclampsia

There is low level evidence for an increased risk of pre-eclampsia in CAYA cancer survivors as compared to controls, as this association was reported in one large population-based Australian study[9] but not in two other studies[11, 13]. Of note, one of these studies concerned a small sub-cohort of 6 CAYA cancer survivors exposed to radiotherapy to the abdomen, none of whom developed pre-eclampsia[13]. No studies were identified that evaluated the risk of pre-eclampsia after chemotherapy.

Maternal anemia

There is low level evidence that abdominopelvic radiotherapy increases the risk of maternal anemia in CAYA cancer survivors as compared to non-irradiated survivors. This is based on increased risks observed in one large study[34] while the effect was not observed in another equally-sized cohort[11].

Gestational diabetes

There is low level evidence overall for an increased risk of gestational diabetes in CAYA cancer survivors as compared to controls, based on one report that found the association[9] and two that did not show an association[11, 35]. There is low level evidence for an effect of abdominopelvic radiotherapy[9, 11, 34, 35], moderate level evidence that there is no effect of chemotherapy, [9, 11, 35] and high level evidence that there is no effect of age at diagnosis[9, 11, 34] on the risk of gestational diabetes.

Malposition of the fetus

There is no increased risk of malposition of the fetus (low level evidence), and no effect of radiotherapy on this outcome (very low level evidence)[10, 34].

Evidence for gestational length and birth weight

Premature birth

CAYA cancer survivors are at increased risk of premature birth (before 37 weeks of gestation) as compared to siblings and the general population (moderate level evidence)[9-13, 27, 28, 35]. High level evidence showed that radiotherapy to volumes exposing the uterus increases the risk of premature birth[9, 11, 13, 28, 34, 35]. Two reports did not delineate specific radiotherapy volumes, categorizing groups only as treated with or without any type of

radiotherapy; but both also showed increased risk after treatment with radiotherapy[9, 11]. We found low level evidence for a dose response relationship with radiotherapy, including one study that showed a trend for increasing risk with increasing flank radiation dose, specifically with doses >15 Gy[14]. Another study showed increased risks specifically with doses >5 Gy to the uterus and in a smaller sub-cohort treated prior to menarche, an even lower threshold of 2.5 Gy[12]. One study showed that chemotherapy was associated with an increased risk of premature birth (low level evidence)[11]. However, this effect was not found in a small Japanese study[35] or in a large Australian population-based study[9]. One study did not observe a significant effect of alkylating agent dose on risk of premature birth (very low level evidence)[12].

Low birth weight

There is moderate level evidence for an increased risk of low birth weight (below 2500 grams) delivery in CAYA cancer survivors as compared to controls[9-13, 27, 35] and high level evidence for this outcome after radiotherapy to volumes exposing the uterus[9, 11, 13, 28, 30, 34, 35]. A dose response relationship was observed in survivors of Wilms tumor[31] and risk of an effect of radiotherapy was observed after >2.5 Gy[12] to the uterus and >25 Gy[30] abdominopelvic radiotherapy (moderate level evidence)[12, 30]. While three studies did not identify chemotherapy as a risk factor for low birth weight[9, 30, 35], the association was suggested in one report[11](very low level evidence). There also seems to be no effect of alkylating agent dose (very low level evidence) on the risk of giving birth to a child with a low birth weight[12].

Small for gestational age

There is low level evidence for no increased risk of small for gestational age (SGA; <10th percentile birth weight for gestational age) delivery among CAYA cancer survivors in general as compared to controls[11, 12, 35]. Although radiotherapy versus no radiotherapy was not found to be significantly associated with this outcome in four studies[13, 28, 30, 35], two studies showed that patients treated with specific doses of abdominopelvic radiotherapy (>5 Gy and >25 Gy, respectively) did have an increased risk (low level evidence)[12, 30].

Evidence for mode of delivery

Vaginal delivery

There is high level evidence indicating that rates of spontaneous vaginal births are lower in CAYA cancer survivors compared to controls[8, 10]. There was no significant difference between survivors and controls (moderate level evidence)[8, 10, 13], and no significant effect of radiotherapy (very low level evidence)[13] on occurrence of assisted vaginal delivery.

Cesarean delivery

There is low level evidence for higher rates of "any cesarean section" (data from reports that did not distinguish between elective (primary) and emergency (secondary/urgent) cesarean sections) among CAYA cancer survivors as compared to controls[9-11, 35], including reports evaluating prevalence after radiotherapy and chemotherapy (low level evidence)[9, 35].

High level evidence was identified for an increased rate of an elective cesarean delivery[8, 10, 11, 34], especially after abdominopelvic radiotherapy (moderate level evidence)[34]. No significantly increased rate was observed for the occurrence of emergency cesarean delivery (moderate level evidence)[8, 10, 13, 34]. Radiotherapy nor age at diagnosis significantly affected the rate of emergency cesarean section (high level evidence)[8, 13, 34]

Evidence for risks related to delivery

Postpartum hemorrhage

There is low level evidence for an increased risk of postpartum hemorrhage in CAYA cancer survivors as compared to controls. An increased risk was observed in one report[8] but not in four others[9, 10, 13, 34]. There is low level evidence for a statistically significant effect of abdominal radiotherapy for this outcome based on one small study suggesting an increased risk [13], while another larger study did not find an increased risk[34].

Evidence for problems of the neonate

Congenital anomalies

There is high level evidence that there is no increased risk of congenital anomalies among neonates of CAYA cancer survivors as compared to controls. Nine studies, with large heterogeneity in outcome definitions, have reported on the prevalence of congenital anomalies and none showed an increased risk[9, 11, 13, 32, 36-40]. There is also high level evidence that there is no significant effect of radiotherapy delivered as part of CAYA cancer therapy on the risk of congenital anomalies[13, 30, 36, 38, 39, 41, 42].

Evidence for additional obstetric outcomes

The evidence levels on the risk of retained placenta/manual removal of the placenta, placental pathologies, fetal growth restriction, uterine scar from previous surgery and perineal laceration/rupture were low to very low or revealed no increased risk for these outcomes. Concerning the neonate, the evidence levels on the risk of resuscitation and admission to a special care unit were very low. Additional outcomes evaluated in a very

limited number of papers are reported in **Appendix 6**, also demonstrating only low to very low levels of evidence.

Translating evidence into recommendations

Final recommendations, formulated based on at least moderate or high levels of evidence for the risk of obstetric outcomes and its determinants **(Table 1)** are summarized in **Table 2**. There was moderate level evidence for an increased risk of miscarriage after radiotherapy to volumes exposing the uterus, and high level evidence for an increased risk of premature birth (<37 weeks of gestation) and low birth weight (<2500 grams) after radiotherapy to volumes exposing the uterus. In addition, CAYA cancer survivors had higher rates of elective cesarean section (high level evidence). There was high level evidence that there is no increased risk of congenital anomalies in the offspring of CAYA cancer survivors. Lower levels of evidence were included for the identification of gaps in knowledge and future research directions **(Panel)**. Radiotherapy was of specific interest if and when a dose-response relationship was identified. Although low level evidence suggests a dose-response relationship of radiotherapy to volumes exposing the uterus with the risk of miscarrriage[29, 30], insufficient evidence is available to identify a safe threshold dose.

For every adverse outcome, the balance between benefits and harms of preconception counseling and surveillance, resource use, acceptability to stakeholders and feasibility or barriers for implementation was considered. The panel agreed that, in general, all female CAYA cancer survivors of reproductive age should be informed by healthcare providers about their potential risk for adverse obstetric outcomes based on cancer treatment exposures (strong recommendation).

For example, female CAYA cancer survivors treated with radiotherapy to volumes exposing the uterus and their health care providers should be aware of the risk of adverse obstetric outcomes including miscarriage (moderate quality evidence), premature birth (high quality evidence) and low birth weight (high quality evidence). In addition, high risk obstetric surveillance is recommended for this patient group (strong recommendations). The panel agreed that the benefits of preconception counseling and obstetric surveillance for these outcomes (i.e., early detection of fetal growth restriction or threatened premature delivery requiring intervention to ensure optimal neonatal outcome) clearly outweigh the potential harms (e.g., stress, anxiety and potential higher health care costs).

Regarding the increased likelihood of elective cesarean section, the panel agreed that no recommendations could be drawn as this risk may be attributable to myriad factors including the survivor's or the healthcare provider's concern.

The absence of an increased risk of congenital anomalies (high quality evidence) is of great importance to survivors and the panel agreed that female CAYA cancer survivors and their health care providers should be aware of this (strong recommendation).

Based on previous recommendations from the IGHG for cardiomyopathy surveillance for CAYA cancer survivors, cardiomyopathy surveillance is reasonable prior to pregnancy or in the first trimester for all female survivors treated with anthracyclines and/or chest radiation (moderate recommendation)[43]. No recommendations have been formulated for the frequency of ongoing cardiomyopathy surveillance in pregnant survivors who have normal left ventricular systolic function immediately prior to or during the first trimester of pregnancy. However, the IGHG panel recommended that health care providers remain alert for cardiomyopathy in survivors treated with anthracyclines and/or chest-directed radiation who present with commonly reported symptoms such as shortness of breath, fatigue, and

ankle swelling[43]. The panel additionally emphasized that CAYA cancer survivors with compromised left ventricular systolic function (<30%) before pregnancy are more likely to have further reduction in cardiac function during pregnancy or post-partum, irrespective of lifetime anthracycline dose[43].

COMMENT

This paper presents the IGHG recommendations for counseling and surveillance of female CAYA cancer survivors before and during pregnancy. Evidence-based recommendations for survivor risk groups were formulated to facilitate consistent long-term follow-up care, optimize the quality of care and minimize burden of disease and unnecessary surveillance. As a result of this effort, the guideline panel also stressed the need for future research in larger cohorts to advance understanding about the radiotherapy dose response relationship to adverse obstetric outcomes.

Critical evaluation of the published literature aided by the GRADE methodology yielded moderate level evidence that CAYA cancer survivors are at increased risk of miscarriage after radiotherapy[9, 23, 24, 26, 28, 29, 31]. When reported, the definition of a miscarriage was heterogeneous (usually pregnancies ending before gestational week 20 or, in the BCCSS, before 24 weeks) and the panel acknowledged the potential for reporting bias in both self-reported and registry-based data. However, increased risks were observed in three large cohorts, from the North American Childhood Cancer Survivor Study (CCSS) (self-reported miscarriage, not further specified[14]), Australia (registered threatened miscarriage after 20 weeks of gestation[9]) and Denmark (registered spontaneous abortion, not further specified[29]). Although low level evidence suggests a dose-response relationship with radiotherapy to volumes exposing the uterus[29, 30], there is insufficient evidence to identify a

safe threshold dose. Even though there is no specific action to reduce this risk, the panel agreed survivors need to be counseled of their potential increased risk of miscarriage.

Lack of definition of termination of pregnancy[14, 29, 32] and broad and overlapping definitions of stillbirth (e.g. the fetus not surviving after 20 weeks of gestation[9], after 28 weeks[29], or combined with neonatal deaths within the first 28 days of life[33]), and potential reporting bias resulted in a low body of evidence on which to base recommendations (**Panel**).

Interestingly, a recent study in survivors aged 39 years or less at cancer diagnosis with robust outcome reporting showed a significantly reduced risk of termination of pregnancy[44], stressing the need for further research to define more accurately the prevalence of this outcome.

We identified high level evidence for the increased risks of premature birth and low birth weight after radiotherapy to volumes exposing the uterus[9-14, 27, 28, 30, 31, 34, 35]. The evidence for dose-response relationships between radiotherapy and miscarriage, premature birth and low birth weight is compelling, but clear evidence to determine a safe threshold dose is lacking. Different approaches have been used to assess radiotherapy dose, giving rise to bias when comparing these studies[12, 27, 29, 30, 45]. In modern clinical practice, approximation of organ-specific radiation exposure parameters that are much closer to the individual true dose distribution during treatment is feasible, and expected to facilitate a more accurate assessment of the relationship of radiation dose and obstetric risks, in future studies.

Radiotherapy to volumes exposing the ovaries, that is, radiotherapy targeting the lower body and thereby exposing the ovaries to substantial amounts of ionizing radiation, is associated with premature ovarian insufficiency[46-49] but does not lead to increased risks of stillbirth or congenital anomalies as compared to the general population. Mechanisms leading to increased rates of miscarriage, premature delivery and low birth weight have not

been completely elucidated, but several hypotheses have been proposed. Radiotherapy to volumes exposing the uterus can damage the uterine vasculature and muscular development[50], and potentially impair endometrial function due to impaired blood supply. This may result in poor implantation of the embryo and poor placental growth which could contribute to subsequent early miscarriage. The increased risks of premature birth and low birth weight may result from uterine vasculature injury leading to impaired utero-placental blood flow, insufficient placental development and hence fetal growth restriction, or may result from a reduced uterine elasticity and volume[50, 51]. Additionally, hormonal deficiency as a consequence of ovarian failure may lead to smaller uterine volumes[51].

Cancer survivors should be counseled about obstetric risks when developmentally and clinically appropriate. Multimorbidity is often the norm in CAYA cancer survivors, emphasizing the need to understand specific treatment-related risks and how collectively these conditions may impact the course of pregnancy. Communication among obstetric and oncology providers and survivors is key in these complicated cases. Preconception consultation and obstetric surveillance may lead to referral to a specialized obstetric team rather than a general obstetric or midwifery team and ensure selection of a hospital for the place of birth rather than a birth center or home. Further clinical management, such as antenatal monitoring for heightened risk of low birth weight or cardiac monitoring, should adhere to established obstetric care guidelines.

No recommendations were formulated based on the high level of evidence concerning the increased likelihood of an elective cesarean section. The increased obstetric risks of cancer survivors may influence the varied clinical, cultural and personal factors for patients and providers that contribute to decision making about elective cesarean sections. Reassuringly,

the likelihood of an emergency cesarean section was not increased among women treated with radiotherapy.

A large and consistent body of evidence indicates that neonates of CAYA cancer survivors treated with and without radiotherapy are not at increased risk of congenital anomalies[13, 30, 36, 38, 39, 41, 42]. As this is often a major concern in CAYA cancer survivors, the panel recommends reassurance of CAYA cancer survivors that there is no indication of such an increased risk.

The recommendations presented here have benefited from the systematic appraisal of bias and transparent implementation of GRADE in assessing the available evidence. Their relevance is further strengthened by the careful considerations that the multidisciplinary and international panel made by extrapolating evidence to recommendations. Some limitations include variability of definitions of outcomes and availability of specific details regarding radiotherapy (dose and site) and chemotherapy (agents and dose) across studies, potential study biases without indication of response rates, and the scarcity of studies with multivariable analyses to address confounding clinical issues. In addition, the body of evidence often indicated no increased risk, but few power calculations were presented in the papers to distinguish between absence of evidence and evidence of absence of an association. We note that we have not addressed thyroid dysfunction in CAYA cancer survivors, an important topic as latent hypothyroidism can impact fetal brain development[15, 16]. Recommendations on surveillance will be formulated in an upcoming IGHG guideline on surveillance of thyroid dysfunction. A periodic update of the obstetric recommendations is planned, and the IGHG thyroid dysfunction surveillance recommendations will then also be included.

The identification of key gaps in knowledge is an important result of the harmonization process (**Panel**). These evidence gaps should be addressed in strong methodical and comprehensive studies from sufficiently large cohorts, or preferably international multicenter collaborative projects to increase generalizability of the results.

CONCLUSION

This IGHG analysis identified specific adverse obstetric related outcomes that are increased in CAYA cancer survivors to characterize the population that will benefit specifically from an individualized preconception consultation and pregnancy surveillance. Key findings are that there are increased risks of premature delivery and low birth weight associated with radiotherapy targeting the lower body and thereby exposing the uterus, which warrant high-risk pregnancy surveillance, and that survivors should be reassured there is no increased risk of congenital abnormality.

Contributors

ALLFK, RLM, LCMK, MMH, MMHE, and JL contributed to the conception and design of the study. All authors contributed to the search strategy, data extractions, interpretations of the data, formulation of the recommendations and critically revised the report. All authors approved the final version.

Acknowledgements

We thank the following people for critically appraising the recommendations and manuscript: expert panel: Melanie Davies, Michael Hawkins, Ann Partridge, Lisa Webber; and patient advocates: Eline van der Meulen and Katie Weyer.

Declaration of interests

The authors have no competing interests to declare.

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687 **Table 1.** Overall conclusions of evidence for obstetric risks in female childhood and adolescent cancer
688 survivors (key outcomes)

Who needs preconception counseling? Who needs high-risk pregnancy surveillance?	
Risk of miscarriage in female cancer survivors diagnosed before age 25 years	**Level of evidence***
No increased risk in CAYA cancer survivors vs controls.	⊕⊕⊕⊖ MODERATE[9, 24, 25, 27, 29, 32]
Increased risk after (*abdominopelvic) radiotherapy* vs. no radiotherapy.	⊕⊕⊕⊖ MODERATE[9, 14, 23-29]
Increased risk with increasing *doses of abdominopelvic and pituitary radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[29, 30]
No significant effect of *chemotherapy* vs. no chemotherapy.	⊕⊕⊕⊖ MODERATE[9, 14, 25, 26, 30]
Increased risk after *chemotherapy and radiotherapy* (no specific field) vs. no chemotherapy and radiotherapy.	⊕⊕⊖⊖ LOW[9, 14, 24, 25, 30]
No significant effect of *age at diagnosis*.	⊕⊕⊖⊖ LOW[9]
Risk of terminations in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased risk in CAYA cancer survivors vs controls.	⊕⊖⊖⊖ VERY LOW[29, 32]
Increased risk after *radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[14, 26]
Increased risk after *chemotherapy* vs. no chemotherapy.	⊕⊖⊖⊖ VERY LOW[14, 26]
Increased risk after chemotherapy and/or radiotherapy (to any field or gonadal) vs. no chemotherapy and radiotherapy.	⊕⊕⊖⊖ LOW[14, 23]
Risk of stillbirth in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased risk in CAYA cancer survivors vs controls.	⊕⊕⊕⊖ MODERATE[9, 29]
No significant effect of *radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[9, 14, 26, 30, 41]
Increased risk after *high-dose ovarian-abdominal radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[30, 33, 41]
Increased risk after *abdominopelvic radiotherapy (>1.00 Gy)* given before menarche vs. no radiotherapy, but no significant effect when given after menarche	⊕⊕⊖⊖ LOW[33]
No significant effect of *chemotherapy* vs. no chemotherapy.	⊕⊕⊖⊖ LOW[9, 14, 26, 30]
No significant effect of *alkylating agent dose*.	⊕⊕⊖⊖ LOW[33]
No significant effect of *alkylating agents in combination with abdominal-pelvic radiation* vs. no alkylating agents and abdominal-pelvic radiation.	⊕⊕⊖⊖ LOW[14, 23, 30]
Risk of gestational hypertension in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased risk in CAYA cancer survivors vs controls.	⊕⊖⊖⊖ VERY LOW[13, 35]
Increased risk after *abdominopelvic radiotherapy* vs. no radiotherapy.	⊕⊖⊖⊖ VERY LOW[13, 34, 35]
Increased risk with *increasing doses of flank radiotherapy* in CAYA Wilms tumor survivors.	⊕⊖⊖⊖ VERY LOW[45]
No significant effect of *chemotherapy* vs. no chemotherapy.	⊕⊖⊖⊖ VERY LOW[35]
No significant effect of age at diagnosis.	⊕⊕⊖⊖ LOW[34]
Risk of pre-eclampsia in female cancer survivors diagnosed before age 25 years	**Level of evidence**
Increased risk in CAYA cancer survivors vs controls.	⊕⊕⊖⊖ LOW[9, 11, 13]
No significant effect of *abdominopelvic radiotherapy* vs. no radiotherapy.	⊕⊖⊖⊖ VERY LOW[13]
Risk of maternal anemia in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased risk in CAYA cancer survivors vs controls.	⊕⊕⊕⊖ MODERATE[9, 11]
Increased risk after *(abdominopelvic) radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[11, 34]
Increased risk after *chemotherapy* vs. no chemotherapy.	⊕⊕⊖⊖ LOW[11]
No significant effect of *radiotherapy and chemotherapy* vs. controls.	⊕⊕⊖⊖ LOW[11]
No significant effect of age at diagnosis.	⊕⊕⊕⊖ MODERATE[11, 34]
Risk of gestational diabetes in female cancer survivors diagnosed before age 25 years	**Level of evidence**
Increased risk in CAYA cancer survivors vs controls.	⊕⊕⊖⊖ LOW[9, 11, 35]
Increased risk after (*abdominopelvic) radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[9, 11, 34, 35]

No significant effect of *chemotherapy* vs. no chemotherapy.	⊕⊕⊕⊖ MODERATE[9, 11, 35]
Increased risk after chemotherapy in combination with radiotherapy vs. controls.	⊕⊖⊖⊖ VERY LOW[9, 11]
No significant effect of age at diagnosis.	⊕⊕⊕⊕ HIGH[9, 11, 34]
Risk of malposition in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased risk in CAYA cancer survivors vs. controls.	⊕⊖⊖⊖ VERY LOW[10]
No significant effect of *radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[34]
Increased risk with *increasing doses flank radiation*.	⊕⊖⊖⊖ VERY LOW[45]
No significant effect of age at diagnosis.	⊕⊕⊕⊕ HIGH[10, 34]
Risk of postpartum hemorrhage in female cancer survivors diagnosed before age 25 years	**Level of evidence**
Increased risk in CAYA cancer survivors vs controls.	⊕⊕⊖⊖ LOW[8-10, 13, 34]
Increased risk after *abdominopelvic radiotherapy* vs. no radiotherapy.	⊕⊖⊖⊖ VERY LOW[13, 34]
No significant effect of age at diagnosis.	⊕⊕⊖⊖ LOW[34]
Risk of premature birth in female cancer survivors diagnosed before age 25 years	**Level of evidence**
Increased risk in CAYA cancer survivors vs. controls.	⊕⊕⊕⊖ MODERATE[9-13, 27, 35]
Increased risk after (*abdominopelvic) radiotherapy* vs. no radiotherapy.	⊕⊕⊕⊕ HIGH[9, 11, 13, 28, 34, 35]
Increased risk with *increasing doses of ovarian-abdominal radiotherapy* (>5/15 Gy).	⊕⊕⊖⊖ LOW[12, 45]
Increased risk after *chemotherapy* vs. no chemotherapy.	⊕⊕⊖⊖ LOW[9, 11, 35]
No significant effect of *alkylating agent dose.*	⊕⊕⊖⊖ LOW[12]
Increased risk after *radiotherapy and chemotherapy* vs. no radiotherapy and chemotherapy.	⊕⊕⊕⊖ MODERATE[9, 11]
Increased risk in *survivors aged >5 yrs at cancer diagnosis* vs. controls, but no significant effect in survivors aged <5 yrs at cancer diagnosis	⊕⊕⊖⊖ LOW[9, 11, 34]
Risk of low birth weight in female cancer survivors diagnosed before age 25 years	**Level of evidence**
Increased risk in CAYA cancer survivors vs controls.	⊕⊕⊕⊖ MODERATE[9-13, 27, 35]
Increased risk after (*abdominopelvic) radiotherapy* vs. no radiotherapy.	⊕⊕⊕⊕ HIGH[9, 11, 13, 28, 30, 34, 35]
Increased risk after *increasing doses of abdominopelvic radiotherapy* (>2.5/25 Gy)	⊕⊕⊕⊖ MODERATE[12, 27, 30, 45]
Increased risk after *chemotherapy* vs. no chemotherapy.	⊕⊖⊖⊖ VERY LOW[9, 11, 30, 35]
No significant effect alkylating agent dose.	⊕⊖⊖⊖ VERY LOW[12]
Increased risk after *radiotherapy and chemotherapy* vs. no radiotherapy and chemotherapy.	⊕⊖⊖⊖ VERY LOW[9, 11, 30]
Increased risk in *survivors aged ≥20 yrs at cancer diagnosis* vs. controls, but no significant effect in survivors aged <20 yrs at cancer diagnosis	⊕⊖⊖⊖ VERY LOW[9, 11, 34]
Risk of delivery of a child small for gestational age in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased risk in CAYA cancer survivors vs. controls.	⊕⊕⊖⊖ LOW[11, 12, 35]
No significant effect of (*abdominopelvic) radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[13, 28, 30, 35]
Increased risk after *increasing doses of abdominopelvic radiotherapy*.	⊕⊕⊖⊖ LOW[12, 30]
No significant effect of *chemotherapy* vs. no chemotherapy.	⊕⊖⊖⊖ VERY LOW[35]
No significant effect of alkylating agent dose.	⊕⊕⊖⊖ LOW[12]
No significant effect of radiotherapy and chemotherapy vs. surgery only.	⊕⊖⊖⊖ VERY LOW[30]
Risk of intrauterine growth restriction in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased risk in CAYA cancer survivors vs. controls.	⊕⊖⊖⊖ VERY LOW[9]
Likelihood of vaginal delivery in female cancer survivors diagnosed before age 25 years	**Level of evidence**
Decreased likelihood of vaginal birth in in CAYA cancer survivors vs. controls.	⊕⊕⊕⊕ HIGH[8, 10]
Likelihood of assisted vaginal delivery in female cancer survivors diagnosed before	**Level of evidence**

age 25 years	
No increased likelihood of in CAYA cancer survivors vs. controls.	⊕⊕⊕⊖ MODERATE[8, 10, 13]
No significant effect of *radiotherapy* vs. no radiotherapy.	⊕⊖⊖⊖ VERY LOW[13]
No significant effect of age at diagnosis.	⊕⊕⊖⊖ LOW[10]
Risk of any cesarean section in female cancer survivors diagnosed before age 25 years	**Level of evidence**
Increased likelihood of any cesarean section in in CAYA cancer survivors vs controls.	⊕⊕⊖⊖ LOW[9-11, 35]
Increased likelihood after *radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[9, 35]
Increased likelihood after *chemotherapy* vs. no chemotherapy,	⊕⊕⊖⊖ LOW[9, 35]
Significant effect of age at diagnosis (increased effect if 0-14 yrs at diagnosis)	⊕⊖⊖⊖ VERY LOW[9, 10]
Likelihood of an elective/primary cesarean section in female cancer survivors diagnosed before age 25 years	**Level of evidence**
Increased likelihood in CAYA cancer survivors vs controls.	⊕⊕⊕⊕ HIGH[8, 10, 11, 34]
Increased likelihood after *radiotherapy* vs. no radiotherapy, specifically after abdominal radiotherapy in Wilms survivors.	⊕⊕⊕⊖ MODERATE[34]
No significant effect of age at diagnosis.	⊕⊕⊕⊕ HIGH[34]
Likelihood of an emergency/secondary/urgent cesarean section in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased likelihood in CAYA cancer survivors vs controls.	⊕⊕⊕⊖ MODERATE[8, 10, 13, 34]
No significant effect of *radiotherapy* vs. no radiotherapy.	⊕⊕⊕⊕ HIGH[13, 34]
No significant effect of age at diagnosis.	⊕⊕⊕⊖ MODERATE[8, 34]
Risk of congenital anomalies/abnormalities in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased risk in CAYA cancer survivors vs controls.	⊕⊕⊕⊕ HIGH[9, 11, 13, 32, 36-40]
No significant effect of (*ovarian-abdominal) radiotherapy* vs. no radiotherapy.	⊕⊕⊕⊕ HIGH[13, 30, 36, 38, 39, 41, 42]
No significant effect of radiotherapy dose.	⊕⊕⊕⊖ MODERATE[30, 36, 41, 42, 45]
No significant effect of *alkylating agents* vs. no alkylating agents.	⊕⊕⊕⊖ MODERATE[30, 38, 39, 41, 42, 52]
No significant effect of alkylating agent dose.	⊕⊖⊖⊖ VERY LOW[42]
No significant effect of *alkylating agents in combination with abdominal-pelvic radiation* vs. no alkylating agents and abdominal-pelvic radiation.	⊕⊕⊕⊖ MODERATE [23, 30, 41]
No significant effect of age at diagnosis.	⊕⊖⊖⊖ VERY LOW[39]
Rate of supervision of high-risk pregnancy in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased rates in CAYA cancer survivors vs controls.	⊕⊕⊖⊖ LOW[34]
No significant effect of *radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[34]
Risk of retained placenta/manual removal of the placenta in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased risk in CAYA cancer survivors vs. controls.	⊕⊕⊖⊖ LOW[9, 13]
Risk of placental pathologies in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased risk in CAYA cancer survivors vs. controls.	⊕⊖⊖⊖ VERY LOW[10]
Risk of resuscitation of the neonate born to female cancer survivors diagnosed before age 25 years	**Level of evidence**
Increased risk in CAYA cancer survivors vs. controls.	⊕⊖⊖⊖ VERY LOW[9]
Likelihood of admission to a special care unit in neonates born to female cancer survivors diagnosed before age 25 years	**Level of evidence**
Increased likelihood in CAYA cancer survivors vs. controls.	⊕⊖⊖⊖ VERY LOW[9]

*Citations refer to papers on which the GRADE level of evidence was based on, and do not necessarily support the overall conclusion.

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692 **Table 2. Harmonized recommendations for counseling and surveillance in pregnancy**

General recommendation
Health care providers should discuss the risk of adverse obstetric outcomes based on the specific cancer treatment exposures with all female CAYA cancer survivors of reproductive age.
Who needs preconception counseling?
Female CAYA cancer survivors and their health care providers should be aware that there is no evidence to support that survivors have an increased risk of giving birth to a child with congenital anomalies (high quality evidence).
Female CAYA cancer survivors treated with radiotherapy to volumes exposing the uterus and their health care providers should be aware of the risk of adverse obstetric outcomes including miscarriage (moderate quality evidence), premature birth (high quality evidence) and low birth weight (high quality evidence).
Who needs specific obstetric surveillance during pregnancy?
High risk obstetric surveillance is recommended for CAYA cancer survivors treated with radiotherapy to volumes exposing the uterus due to the risk of premature birth and low birth weight (high quality evidence).

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Who needs specific cardiac surveillance during pregnancy? *Based on IGHG cardiomyopathy guideline*[43]
Cardiomyopathy surveillance is reasonable prior to pregnancy or in the first trimester for all female survivors treated with anthracyclines and/or chest radiation (moderate level recommendation, moderate quality evidence)[43].
No recommendations can be formulated for the frequency of ongoing surveillance in pregnant survivors who have normal left ventricular systolic function immediately prior to or during the first trimester of pregnancy (moderate level recommendation, low quality evidence)[43].

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Panel: Gaps in knowledge and future directions for research of obstetric outcomes in CAYA cancer survivors

- Risks of medical and elective termination of pregnancy following CAYCA cancer, including standardized definitions of this outcome and its confounders
- Risks of gestational diabetes, gestational hypertension and pre-eclampsia, giving birth to babies small for gestational age, very premature delivery (<32 weeks of gestation) or postpartum hemorrhage
- Effect of radiotherapy and dose-response relationships to specific volumes (e.g., uterus) on obstetric outcomes
- Influence of relatively low doses of radiotherapy (including 10-15 Gy) that reach the uterus on obstetric outcomes
- Effect of age at cancer diagnosis and pubertal stage at treatment on all obstetric risks
- The contribution of environmental factors known to affect obstetric outcomes (e.g., BMI, smoking)
- The contribution of obstetric risk associated with artificial reproductive technology (ART), especially as fertility rates after ART (including donor oocytes) increase
- Development of a risk prediction algorithm for outcomes including miscarriage, premature delivery and low birth weight, taking into account, e.g., age at cancer diagnosis, cancer treatment, maternal age, smoking, parity and ART
- Methods to optimize timely provision of information about obstetric risk to CAYA cancer survivors in a variety of health care systems and health literacy settings
- The effect of high risk surveillance on clinical relevant outcomes for survivors at risk

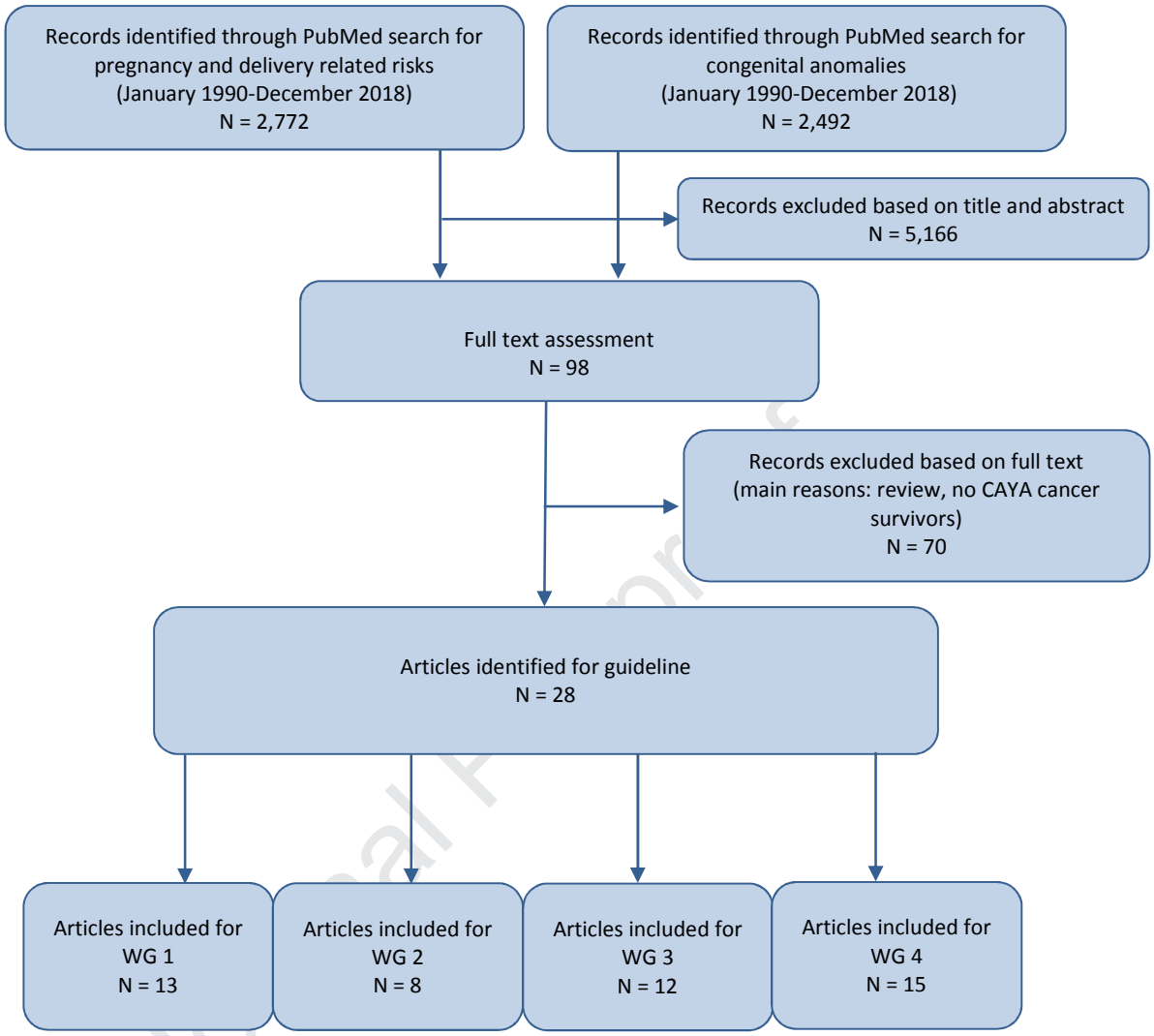

Figure 1. Flowchart of selected studies. Articles could be included for multiple working groups (WG). Four working groups respectively evaluated the following topics: 1) adverse fetal outcomes in pregnancy (such as miscarriage); 2) adverse maternal outcomes in pregnancy; 3) delivery outcomes; and 4) congenital anomalies of the neonate.